

Direct and Enantioselective Organocatalytic α -Chlorination of Aldehydes

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Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.¹ Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chloroform was distilled from calcium hydride prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on Iatrobeads 6RS–8060 according to the method of Still.² Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or anisaldehyde stain. Gas liquid chromatography (GLC) assays to determine enantiometric excess were developed using racemic samples.

¹H and ¹³C NMR spectra were recorded on Varian Mercury 300 (300 MHz and 75 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ¹H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ¹³C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm⁻¹). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 Series gas chromatography equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex α -TA (30 m 0.25 mm) column.

General Procedure: A 10 mL round-bottom flask equipped with a magnetic stir bar and charged with (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (16.6 mg, 0.05

mmol) and acetone (2 mL) is allowed to cool to $-30\text{ }^{\circ}\text{C}$ for five minutes prior to addition of 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (361 mg, 1.2 mmol). The aldehyde substrate (1 mmol) was added to the yellow homogenous solution. The resulting mixture was stirred at $-30\text{ }^{\circ}\text{C}$ until the reaction is determined to be complete by GLC, upon which time the mixture is a pale yellow heterogeneous solution. The reaction was then eluted with Et_2O and passed through Iatrobeds (8 g), and the resulting organics were carefully concentrated *in vacuo* (using an ice bath). The resulting residue was purified by Iatrobeds chromatography (solvents noted) and organics carefully concentrated *in vacuo* with an ice bath to provide the title compounds. The enantioselectivity was determined by chiral GLC analysis.

5-Methoxymethoxy-pentanal: To a flask containing 1,5-pentanediol (34 mL, 330 mmol) and NEt_3 (13.7 mL, 99 mmol) in CH_2Cl_2 (150 mL) was slowly added chloromethyl methyl ether (5.0 mL, 65.8 mmol) at $0\text{ }^{\circ}\text{C}$. The solution was allowed to warm to room temperature and stirred for 4 hours. The reaction was then treated with saturated aqueous NH_4Cl , extracted with CH_2Cl_2 (2 \times 100 mL), dried over Na_2SO_4 , and concentrated. Iodobenzene diacetate (8.4 g, 26.2 mmol) was then added to a solution of the crude product (3.5 g, 24 mmol) and TEMPO (0.37 g, 2.4 mmol) in CH_2Cl_2 (50 mL).³ The reaction was stirred for 12 hours and then diluted with CH_2Cl_2 (250 mL). The mixture was washed with a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (150 mL) and extracted with CH_2Cl_2 (2 \times 100 mL). The combined organics were washed with saturated aqueous NaHCO_3 (150 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The resulting residue is purified by silica gel chromatography (40% Et_2O / pentane) and the organics carefully concentrated *in vacuo* with an ice bath to provide the title compound. IR (film) 2941, 2871, 2720, 1725, 1454, 1383, 1353, 1262, 1201, 1138, 1122, 1078, 1035, 991.9, 905.0, 868.3, 814.2 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.74 (t, 1H, $J = 1.5\text{ Hz}$, CHO), 4.58 (s, 2H, CH_2OMe), 3.51 (t, 2H, $J = 6.5\text{ Hz}$, $\text{CH}_2\text{CH}_2\text{O}$), 3.33 (s, 3H, CH_3), 2.46 (td, $J = 1.5, 7.3\text{ Hz}$, 2H), 1.76- 1.54 (m, 4H, $(\text{CH}_2)_2\text{CH}_2\text{CHO}$); ^{13}C NMR (75 MHz, CDCl_3) δ 202.3, 96.4, 67.1, 55.1, 43.5, 29.1, 18.9; HRMS (CI) exact mass calculated for $(\text{C}_7\text{H}_{13}\text{O}_3)$ requires $m-1/z$ 145.0865, found $m-1/z$ 145.0862.

(S)-2-Chloro-octanal (Table 3, entry 1): Prepared according to the general procedure from octylaldehyde (156 μ L, 1.00 mmol) for 6 h to provide the title compound as a colorless oil (115.2 mg, 71% yield, 92% ee) after Iatrobeds chromatography (2.5% Et₂O/ pentane). IR (film) 3385, 2957, 2927, 2858, 1458, 1400, 1378, 1343, 1138, 1102, 1069, 879.9 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.52 (d, 1H, *J* = 2.7 Hz CHO), 4.19 (ddd, 1H, *J* = 2.7, 5.6, 8.2 Hz, CHCl), 2.06- 1.95 (m, 1H, ClCCH₂), 1.90- 1.79 (m, 1H, ClCCH₂), 1.62- 1.26 (m, 8H, (CH₂)₄CH₃), 0.92 (t, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 195.4, 64.0, 32.1, 31.5, 28.6, 25.5, 22.5, 14.0; HRMS (CI) exact mass calculated for (C₈H₁₅ClO) requires *m/z* 162.0811, found *m/z* 167.0812. $[\alpha]_D^{25} = -35.47$ (*c* = 1.0, CHCl₃). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex β -TA (30 m x 0.25 mm) column (50 °C isotherm, 1 mL/min); (*R*) isomer *t_r* = 75.5 min and (*S*) isomer *t_r* = 81.4 min.

(S)-2-Chloro-7-octenal (Table 3, entry 2): Prepared according to the general procedure from oct-7-enal (126 mg, 1.00 mmol) for 8 h to provide title compound as a colorless oil (114 mg, 76% yield, 92% ee) after Iatrobeds chromatography (2% Et₂O/ pentane). IR (film) 3853, 3676, 3406, 2970, 2928, 2855, 2357, 2325, 1279, 1102, 1076, 905.2 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.45 (d, 1H, *J* = 2.2 Hz, CHO), 5.83-5.69 (m, 1H, CH₂CH=CH₂), 4.97 (dd, 2H, *J* = 1.7, 10.1 Hz, CH=CH₂), 4.13 (ddd, 1H, *J* = 2.2, 6.7, 7.1 Hz, CHCl), 2.09-1.99 (m, 2H, CH₂CH=CH₂), 2.02-1.93 (m, 1H, ClCCH₂), 1.88-1.76 (m, 1H, ClCCH₂), 1.62-1.38 (m, 4H, CH₂(CH₂)₂CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 195.5, 138.4, 115.1, 64.1, 33.5, 32.1, 28.4, 25.2; HRMS (CI) exact mass calculated for (C₈H₁₃ClO) requires *m/z* [M-Cl] = 127.0759, found *m/z* 127.0759. $[\alpha]_D^{25} = -40.59$ (*c* = 1.0, CHCl₃). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex β -TA (30 m x 0.25 mm) column (50 °C isotherm, 1 mL/min); (*R*) isomer *t_r* = 89.3 min and (*S*) isomer *t_r* = 91.4 min.

(S)-Chloro-cyclohexyl-acetaldehyde (Table 3, entry 3): Prepared according to the general procedure from cyclohexyl-acetaldehyde³ (138 μ L, 1.00 mmol) for 8 h to provide the title compound as a colorless oil (139.8 mg, 87% yield, 94% ee) after Iatrobeds chromatography (2.5% Et₂O/ pentane). IR (film) 3374, 2930, 2855, 1451,

1378, 1112, 1080, 890.3, 733.0 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.50 (d, 1H, $J = 3.5$ Hz, CHO), 4.00 (dd, 1H, $J = 3.5, 6.4$ Hz, CHCl), 2.07- 1.92 (m, 1H, ClCCH), 1.90- 1.66 (m, 4H), 1.43- 1.11 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 195.8, 69.4, 40.2, 29.7, 28.3, 25.9, 25.8, 25.6; HRMS (CI) exact mass calculated for ($\text{C}_7\text{H}_{12}\text{Cl}$) requires m/z 131.0628, found m/z 131.0626. $[\alpha]_{\text{D}} = -6.01$ ($c = 1.0$, CHCl_3). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex β -TA (30 m x 0.25 mm) column (60 $^\circ\text{C}$ isotherm, 1 mL/min); (*R*) isomer $t_{\text{r}} = 101.3$ min and (*S*) isomer $t_{\text{r}} = 111.0$ min.

(*S*)-Chloro-tricyclo[3.3.1.1^{0,0}]dec-1-yl-acetaldehyde (Table 3, entry 4):

Prepared according to the general procedure from tricyclo[3.3.1.1^{0,0}]dec-1-yl-acetaldehyde⁴ (174 μL , 1.00 mmol) at -40 $^\circ\text{C}$ using (*5S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (66.4 mg, 0.2 mmol) for 24 h to provide the title compound as a colorless oil (136.5 mg, 85% yield, 95% ee). The excess 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one was consumed by addition of propionaldehyde (29 μL , 0.40 mmol). The reaction was quenched by filtration through Iatrobeds (8 g) eluting with Et_2O and concentrated *in vacuo*. The resulting residue was purified by Iatrobeds chromatography (2.5% Et_2O / pentane). IR (film) 2905, 2851, 1730, 1456, 1345, 1106, 1064, 1004, 976.2, 762.9 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.52 (d, 1H, $J = 4.8$ Hz, CHO), 3.70 (d, 1H, $J = 4.8$ Hz, CHCl), 2.10- 2.02 (m, 3H), 1.81-1.63 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 195.7, 73.8, 38.8, 37.1, 36.5, 28.0; HRMS (CI) exact mass calculated for ($\text{C}_{12}\text{H}_{17}\text{ClO}$) requires m/z 212.0968, found m/z 212.0970. $[\alpha]_{\text{D}} = +30.02$ ($c = 1.0$, CHCl_3). Reduction of the title compound to the corresponding alcohol and cyclization with aqueous 50% KOH provided the epoxide 2-tricyclo[3.3.1.1^{0,0}]dec-1-yl-oxirane which matched literature data.⁵ The enantiomeric ratio of the epoxide was determined by GLC using a Bodman Chiraldex β -TA (30 m x 0.25 mm) column (100 $^\circ\text{C}$ isotherm, 1 mL/min); (*S*) isomer $t_{\text{r}} = 49.3$ min and (*R*) isomer $t_{\text{r}} = 51.6$ min.

(*S*)-2-Chloro-hydrocinnamaldehyde (Table 3, entry 5): Prepared according to the general procedure from hydrocinnamaldehyde (62 mg, 0.50 mmol) in d_6 -acetone for 6 h. To reaction flask was added benzyl methyl ether (61 mg, 0.50 mmol). The title compound was provided (92% NMR yield, 92% ee) then isolated as a colorless oil (80%

ee) after Iatrobeds chromatography (2% Et₂O/ pentane). The title compound was identical in all respects to the known literature compound with regards to NMR and HRMS data.⁶ IR (film) 3511, 2360, 2341, 1717, 1653, 1540, 1417, 1377, 1277, 1191, 1111, 767.7, 701.6 cm⁻¹; [α]_D = -8.84 (c = 1.0, CHCl₃). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex β -TA (30 m x 0.25 mm) column (60 °C isotherm, 1 mL/min); (R) isomer t_r = 234.3 min and (S) isomer t_r = 245.4 min.

(S)-2-Chloro-5-methoxymethoxy-pentanal (Table 3, entry 6): Prepared according to the general procedure from 5-methoxymethoxy-pentanal (170 μ L, 1.00 mmol) at -40 °C for 12 h to provide the title compound as a colorless oil (139.8 mg, 94% yield, 93% ee) after Iatrobeds chromatography (40% Et₂O/ pentane). IR (film) 3401, 2932, 2885, 2826, 1736, 1445, 1386, 1346, 1149, 1110, 1040, 919.5, 775.0 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.53 (d, 1H, *J* = 2.1 Hz, CHO), 4.62 (s, 2H, CH₂OMe), 4.26 (ddd, 1H, *J* = 2.1, 5.1, 8.5 Hz, CHCl), 3.59 (t, 2H, *J* = 5.8 Hz, CH₂CH₂O), 3.37 (s, 3H, CH₃), 2.22- 2.09 (m, 1H), 2.00- 1.68 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 195.0, 96.4, 66.5, 63.7, 55.3, 29.1, 25.8; HRMS (CI) exact mass calculated for (C₇H₁₄ClO₃) requires *m/z* 181.0632, found *m/z* 181.0632. [α]_D = -12.68 (c = 1.0, CHCl₃). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex β -TA (30 m x 0.25 mm) column (50 °C isotherm, 1 mL/min); (R) isomer t_r = 260.4 min and (S) isomer t_r = 267.5 min.

(S)-2-Chloro-6-oxo-heptanal (Table 3, entry 7): Prepared according to the general procedure from 6-oxo-heptanal⁷ (128 mg, 1.0 mmol) for 12 h to provide title compound as a colorless oil (134 mg, 78% yield, 87% ee) after Iatrobeds chromatography (35% Et₂O/ pentane). IR (film) 3420, 2933, 2855, 2360, 1732, 1715, 1418, 1363, 1162 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.47 (d, 1H, *J* = 2.3 Hz, CHO), 4.16 (dd, 1H, *J* = 2.2, 7.2 Hz, CHCl), 2.47 (t, 2H, *J* = 7.2 CH₂CO), 2.12 (s, 3H, CH₃), 2.03-1.93 (m, 1H), 1.85-1.57 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 207.9, 195.1, 63.8, 42.7, 31.4, 30.1, 19.9; HRMS (CI) exact mass calculated for (C₇H₁₅ClO₂) requires *m/z* =160.0655, found *m/z* 160.0658. [α]_D = -49.93 (c = 1.0, CHCl₃). The enantiomeric ratio

was determined by GLC using a Bodman Chiraldex β -TA (30 m x 0.25 mm) column (75 °C isotherm, 1 mL/min); (*R*) isomer t_r = 144.1 min and (*S*) isomer t_r = 149.3 min.

(*R*)-2-Chloro-(*R*)-3-phenylbutyraldehyde (Equation 3): Prepared according to the general procedure from (*S*)-3-phenylbutyraldehyde (74 mg, 0.50 mmol) for 6 h to provide the title compound as a colorless oil (65 mg, 71% yield, 7:1 *anti:syn*, 98% ee) after Iatrobeds chromatography (1% Et₂O/ pentane). IR (film) 3821 3751, 2973, 2831, 1733, 1495, 1455, 762.5, 700.0 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.37 (d, 1H, *J* = 3.0 Hz, CHO), 7.37-7.23 (m, 5H, ArH), 4.29 (dd, 1H, *J* = 3.0, 6.6 Hz, CHCl), 3.47 (qd, *J* = 6.6, 7.2 Hz, 1H, CHCH₃), 1.46 (d, *J* = 7.2 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 195.2, 140.3, 129.9, 128.8, 128.5, 128.4, 127.9, 127.7, 68.7, 42.3, 18.7; HRMS (CI) exact mass calculated for (C₁₀H₁₁ClO) requires *m/z* = 182.0502, found *m/z* 182.0498. $[\alpha]_D^{25}$ = -3.86 (*c* = 1.0, CHCl₃). Product ratio was determined by GLC using a Bodman Chiraldex β -TA (30 m x 0.25 mm) column (75 °C isotherm, 1 mL/min); *anti* adduct (2*R*, 3*R*) t_r = 115.5 min, *syn* adduct (2*S*, 3*R*) t_r = 189.2 min.

(*S*)-2-Chloro-(*R*)-3-phenylbutyraldehyde (Equation 4): Prepared according to the general procedure from (*S*)-3-phenylbutyraldehyde (74 mg, 0.50 mmol) for 6 h to provide pure title compound as a colorless oil (72 mg, 79% yield, 24:1 *syn:anti*, 98% ee) after Iatrobeds chromatography (1% Et₂O/ pentane). IR (film) 3821 3751, 2973, 2831, 1733, 1495, 1455, 762.5, 700.0 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.37 (d, 1H, *J* = 3.0 Hz CHO), 7.37-7.23 (m, 5H, ArH), 4.29 (dd, 1H, *J* = 3.0, 6.6 Hz, CHCl), 3.47 (qd, 1H, *J* = 6.6, 7.2 Hz, CHCH₃), 1.4 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 195.2, 140.3, 129.9, 128.8, 128.5, 128.4, 127.9, 127.7, 68.7, 42.3, 18.7; HRMS (CI) exact mass calculated for (C₁₀H₁₁ClO) requires *m/z* = 182.0502, found *m/z* 182.0498. $[\alpha]_D^{25}$ = -2.31 (*c* = 1.0, CHCl₃). The enantiomeric and diastereomeric ratios were determined by GLC using a Bodman Chiraldex β -TA (30 m x 0.25 mm) column (75 °C isotherm, 1 mL/min); *syn* adduct (2*S*, 3*R*) t_r = 111.8, *anti* adduct (2*R*, 3*R*) t_r = 190.2 min.

Stereochemical Analysis

Procedure for Conversion to Epoxide: To a solution of (*S*)-2-chloroaldehyde (0.5 mmol) in CH₂Cl₂ (0.5 mL) and absolute ethanol (0.5 mL) was added sodium borohydride (0.5 mmol) at 0 °C. After 15 min, the resulting solution was treated with saturated aqueous NaHCO₃ and the mixture was extracted with CH₂Cl₂. The crude mixture was then concentrated *in vacuo*. The resultant yellow oil was then added to a round-bottom flask equipped with a magnetic stir bar. To the flask was added a solution of aqueous 50% KOH (2 mL) and allowed to stir at room temperature for 4 hours. At this time the resulting mixture was washed with Et₂O (3 x 5 mL) before the organics were concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (5% Et₂O/ pentane).

(*R*)-Benzyl oxirane: Prepared according to the procedure for conversion to epoxide from (*S*)-2-chloro-hydrocinnamaldehyde (77 mg, 0.5 mmol) to afford the title compound as a colorless oil (37 mg, 55% yield). The title compound was identical in all respects to the known literature compound. $[\alpha]_D = +10.1$ ($c = 1.94$, EtOH); reported rotation for (*S*)-benzyl oxirane $[\alpha]_D = -17.3$ ($c = 1.94$, EtOH).⁸

(*R*)-2-Hexyloxirane: Prepared according to the procedure for conversion to epoxide from (*S*)-2-chloro-octanal (81 mg, 0.5 mmol) to afford the title compound as a colorless oil (42 mg, 66% yield). The title compound was identical in all respects to the known literature compound. $[\alpha]_D = +6.2$ ($c = 1.8$, CHCl₃); reported rotation for (*R*)-2-hexyloxirane $[\alpha]_D = +7.4$ ($c = 4.5$, CHCl₃).⁹

(*R*)-2-Cyclohexyloxirane: Prepared according to the procedure for conversion to epoxide from (*S*)-chloro-cyclohexyl-acetaldehyde (80 mg, 0.5 mmol) to afford the title compound as a colorless oil (24 mg, 38% yield). The title compound was identical in all respects to the known literature compound. $[\alpha]_D = -2.1$ ($c = 0.88$, CHCl₃); reported rotation for (*S*)-2-cyclohexyloxirane $[\alpha]_D = +2.1$ ($c = 0.88$, CHCl₃).¹⁰

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